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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/814,891	03/31/2004	Maurice Arthur Trewhella	GRH0105PUSA	7582
22045	7590	04/27/2007		
BROOKS KUSHMAN P.C. 1000 TOWN CENTER TWENTY-SECOND FLOOR SOUTHFIELD, MI 48075			EXAMINER HA, JULIE	
			ART UNIT	PAPER NUMBER
			1654	
SHORTENED STATUTORY PERIOD OF RESPONSE		MAIL DATE	DELIVERY MODE	
3 MONTHS		04/27/2007	PAPER	

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

**Office Action Summary**

Application No.

10/814,891

Applicant(s)

TREWHELLA ET AL.

Examiner

Julie Ha

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 March 2007.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 16-22, 24-30 and 34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-15, 23 and 31-33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Response to Election/Restriction filed on March 22, 2007 is acknowledged. Claims 1-34 are pending in this application.

#### ***Restriction***

1. Applicant's election without traverse of Group I (claims 1-33) and species election of ketone, fluoxetine, ibuprofen and propylamine in the reply filed on March 22, 2007 is acknowledged. Claims 16-22, 24-30 and 34 are withdrawn from consideration being drawn to nonelected species (claims 16-22 and 24-30) and nonelected Invention (claim 34). Claims 1-15, 23, and 31-33 are examined on the merits in this office action.

#### ***Rejection-35 U.S.C. 112, 2<sup>nd</sup>***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claims 1 and 12 recite "in the absence of a solvent". It is unclear what "absence of solvent" means. For example, it is unclear if "absence of solvent" means absence of organic solvent only or if means ALL solvents, including water. Claim 12 is further indefinite since it recites "contacting the organic compound with the yeast and water the absence of solvent to form a mixture...adding an organic solvent to the mixture..." It is

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unclear, since water is clearly a "solvent" since it is forming a mixture. However, the claim recites "in the absence of a solvent".

5. Claim 12 recites the limitation "the product" in the 4<sup>th</sup> line of the claim. There is insufficient antecedent basis for this limitation in the claim.

***Rejection-35 U.S.C. 102***

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-2, 10-13 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Howarth et al (Tetrahedron Letters, 2001, 42(42): 7517-7519).

8. The instant claims are drawn to a method of reducing an organic compound (ketone), comprising subjecting the organic compound to a yeast mediated reduction wherein the reduction is conducted in the absence of solvent. Further, the claims are drawn to the method wherein the reduction is conducted in the presence of sufficient water to enable reduction to take place, but insufficient to provide a separate water layer.

9. Howarth et al teach immobilized baker's yeast reduction of ketones in an ionic liquid ([bmim]PF<sub>6</sub>) and water mix (see title). This reads on claims 14-15. The reference teaches that concurrent research on ionic liquids has shown that they support a large and diverse range of organic reaction, these include amongst many others, oxidations,

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coupling reactions, nucleophilic displacements, reductions, and alkylations (see p. 7517, left column 2<sup>nd</sup> paragraph). Furthermore, the reference teaches the whole-cell biotransformation such as yeast-mediated reductions of ketones in an ionic liquid (see p. 7517, right column, 1<sup>st</sup> paragraph). Further, the reference teaches that the inactivation of enzymes in organic solvents can be avoided if the enzyme is surrounded by a layer of water (this reads on claim 2), thus a quantity of water was added to the ionic liquid...and immobilized baker's yeast was also utilized with addition of methanol as an energy source (see p. 7517, right column, 1<sup>st</sup> paragraph, lines 5-23). The yeast-mediated reduction of ketones is shown in Table 1 (see p. 7516). This meets the limitation of claims 1-2. The reference further teaches that whilst the reactions may be carried out in the absence of water, the yields and enantiomeric excesses were extremely poor, probably because of the inactivation of the enzyme within the yeast responsible for the reduction (see p. 7519, 1<sup>st</sup> paragraph, lines 5-10). This reads on claim 2. Furthermore, the reference teaches that the ionic liquid and water were mixed together and warmed to a temperature of 33°C and at atmospheric pressure...the whole system was stirred for a further 1 h, the ketone added...the extracts were combined and dried, filtered and the solvent was removed in vacuo (see p. 7519, Bioreduction reaction procedure). This reads on claims 10-13. Additionally, the reference teaches Table 1, compound 5. This reads on claim 15, as an activated ketone since an activated ketone in the arts is known as being susceptible to nucleophilic attack (see "Active-site directed modifying reagents or affinity labels", Chem 231 Lecture No. 10 Sp 1999).

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10. Claims 1, 14-15, 23 and 31-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar et al (Tetrahedron Letters, 1991, 32(16): 1901-1904).

11. The instant claims are drawn to a method of reducing an organic compound (ketone), comprising subjecting the organic compound to a yeast mediated reduction wherein the reduction is conducted in the absence of solvent. Further, the claims are drawn to the method wherein the compound is precursor for the synthesis of a pharmaceutical Fluoxetine.

12. Kumar et al teach a new chemoenzymatic synthesis of optically pure (R)-Tomoxetine and both the enantiomers of Fluoxetine (see abstract). The reference teaches baker's yeast reduction of ethyl 3-oxo-3-phenylpropanoate (ketone body) to yield ethyl 3-hydroxy-3-phenylpropionate (alcohol), the step comprising Baker's yeast, glucose, and water (see p. 1901, 3<sup>rd</sup> paragraph and p. 1902, Scheme, step (i)). This reads on claims 1 and 14-15. Further, the reference teaches the synthesis of Fluoxetine (aryl propylamine) (see p. 1902, Scheme, 2a and 2b). This reads on claim 23.

Furthermore, it is well known in the art that Fluoxetine (Prozac<sup>TM</sup>, Eli Lilly Co.) is a potent clinically effective anti-depressant (see p. 1901, 1<sup>st</sup> paragraph, 2<sup>nd</sup> sentence).

Thus, this reads on claims 31-33.

### ***Rejection-35 U.S.C. 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

15. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1 and 3-15 are rejected under 35 U.S.C. 102(b) are being unpatentable over Liu et al (Synthetic Communications, 2001, 31(10): 1521-1526) in view of MPEP 2144.04 C.

17. The instant claims are drawn to a method of reducing an organic compound (ketone), comprising subjecting the organic compound to a yeast mediated reduction wherein the reduction is conducted in the absence of a solvent; and wherein the organic compound is contacted with yeast with water-to yeast ratio between 0.2 ml/g and 1.5 ml/g. The claims are further drawn to the method wherein the reaction is carried out in

nonfermenting conditions at temperatures between 0 to 50°C, at room temperature, and at atmospheric pressure. Additionally, the claims are drawn to adding an organic solvent to the mixture to dissolve the product, and conducting a solid/liquid separation comprising evaporating the solvent to isolate the product of the reaction.

18. Liu et al teach the reduction of aromatic ketones to optically active alcohols, mediated by dried baker's yeast in a small amount of water (0.4 ml/g yeast) in dry petroleum ether at room temperature for 24 h (see abstract). This reads on claims 1, 3-4, 9-11 and 14-15. Since the reaction takes place at room temperature, the reference reads on atmospheric pressure, thus reads on claims 9-11. The reference further teaches that no reaction was observed when aromatic ketones were stirred in dry petroleum ether in the presence of yeast; however, the addition of small amounts of water to the reaction system greatly contributed to the increased reduction of aromatic ketone. The most suitable amount of water was 0.4 mL/ g of yeast. The reference further points out that perhaps larger amounts of water would improve the substrate conversion. Nevertheless, the amount of 0.5 mL water/ g of yeast resulted in obvious swelling and adhesion of dried baker's yeast (see p. 1522, 1<sup>st</sup> paragraph in Effect of Water on Reactivity). The same effect was also observed when the reaction was carried out in chloroform and toluene. The reference further teaches 0.6 g (5 mmol) acetophenone, 2.5 mL water and 5 g yeast and ether was stirred at room temperature, and that the reaction mixture was filtered to remove the yeast; dried over anhydrous magnesium sulfate, the filtrate was concentrated with a rotary evaporator under reduced pressure (see p. 1525, General Procedure for Reduction of Aromatic Ketones). This



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reads on claims 6-8, 12 and 13. Since 2.5 mL water would equal 2.5 g of water, and 5 g of yeast was added, therefore, that would make the water in an amount of 50% w/w on the weight of yeast. Additionally, claim 7 recites that 0.1 gram of yeast per mmol of organic compound (ketone), up to 50 grams of yeast per mmol of organic compound and claim 8 recites that yeast to organic compound is 0.8 to 20 g/mmol. Since 5 g of yeast was added to 5 mmol of acetophenone, this reads that 1g of yeast is equivalent to 1 mmol of ketone. Thus, this reads on claims 7-8. The difference between the reference and the instant claims is that the reference does not teach a method of reducing an ketone in the absence of solvent and then in presence of sufficient water, but teaches the reverse order.

19. Therefore, it would have been obvious to one of the ordinary skill in the art to reverse the orders of reaction of Liu et al. Liu et al teach that no reaction was observed when aromatic ketones were stirred in dry petroleum ether in the presence of yeast at room temperature for 24 h. When a small amount of water was added to the reaction system, this contributed to the increased reduction of aromatic ketone. Furthermore, the reference teaches that it is obvious that the water: yeast ratio indeed affects the reaction significantly. It has been shown that an enzyme molecule becomes fully hydrated when surrounded by a few layers of water molecule, and this hydration layer acts as a micro-reactor for the enzyme and protects it from any detrimental effects of the bulk organic solvent (see p. 1523, 2<sup>nd</sup> paragraph). Since addition of more water (0.5 mL/g of yeast) resulted in swelling and adhesion of dried baker's yeast, but the reference suggests that larger amounts of water would improve the substrate conversion and "hydration layer

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acts as a micro-reactor for the enzyme and protects it from any detrimental effects of the bulk organic solvent", it would have been obvious to reverse the order of the reaction. MPEP states the following: Ex parte Rubin, 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render prima facie obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also In re Burhans, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results); In re Gibson, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is prima facie obvious.). Therefore, there is a reasonable expectation of success, since "selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results."

### ***Conclusion***

20. No claims are allowed.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982.

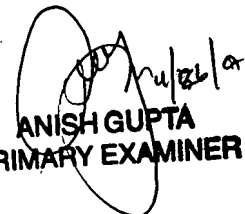
The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

  
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